IN THE SPECIFICATION

Please replace the first paragraph on page 2 with the following paragraph:

clinically diagnosed until after 1-3 weeks. The daily iron requirement for a normal erythropoiesis is 25 mg. Of this only ~~ca.~~ about 1 mg is derived from the food, the main requirement is normally met by re-utilization of the haemoglobin iron after the degradation of aged erythrocytes. The release of iron from the reticular cells is greatly reduced in chronic diseases. The iron is retained in the reticuloendothelial system and is no longer available for erythropoiesis. One therefore also speaks of an "inner iron deficiency" in which normal compensation mechanisms are incompletely triggered. A reticulocytopenia and an absence of a hyperplasia of the erythropoiesis that would be needed to compensate for the anaemia are typical. A reduced erythropoietin secretion or activity may also be an additional pathogenetic factor. A significant change in iron metabolism is for example the absence of a compensatory increase in transferrin formation. The underlying disorder is therefore the lack of iron release from the iron stores (in the reticuloendothelial cells) into the plasma (and thus also into the erythron) as a result of which the normal compensation mechanisms are not triggered. The administration of recombinant erythropoietin is utilized therapeutically to significantly increase the number of erythrocytes.

Please replace the third paragraph on page 3 with the following paragraph:

B2

The bioavailability of the iron can be pathophysiologically disturbed resulting in a reduced iron absorption in the body. Of the approximately 10 mg that is daily available through the diet an adult only absorbs ~~ca.~~ about 1 mg. In iron deficiency the absorption increases, but seldom above 5-6 mg, if no additional iron is supplied. The exact mechanism for the absorption of iron has not been elucidated. The mucosal cells of the small intestine play a decisive role in the regulation. The most important signal for the mucosa appears to be the total iron content of the body. It has been shown that the serum ferritin concentration correlates inversely with the amount of absorbed iron.

Please replace the second paragraph on page 4 with the following paragraph:

B3

Iron that is not required for erythropoiesis is transferred by transferrin into two types of storage pool. Ferritin is the most important store. This is a heterogeneous family of proteins which surround an iron core. It is soluble and represents the active storage form in the liver (hepatocytes), bone marrow, spleen (macrophages), erythrocytes and in the serum (~~ca.~~ about 100 ng/ml). The tissue ferritin pool is very labile and is rapidly available when iron is required. Circulating serum ferritin is derived from the reticuloendothelial system and its circulating concentration parallels that

B3

of the total body iron (each ng/ml corresponds to 8 mg iron store).

Please replace the second paragraph on page 5 with the following paragraph:

B4

The iron stores are considered to be "full" when the serum ferritin is > 150 µg/l and a transferrin saturation of > ~~20 %~~ 20% is present. P. Grützmacher et al. describe in Clinical Nephrology, Vol. 38, No. 1, 1992, p. 92-97 that under these conditions one can assume a maximum response to EPO therapy.

Please replace the second paragraph on page 6 with the following paragraph:

B5

Since the oral iron absorption is only ~~ca.~~ about 1 mg/day and under extreme loading (with an oral administration of ~~ca.~~ about 300 mg Fe (III)/day) is less than 3 mg/day, an intravenous administration of relatively large amounts of iron is increasingly preferred. On the German pharmaceutical market two iron preparations are at present available that can be administered intravenously. These are the drugs "Ferrlecit" and "Ferrum Vitis". Ferrlecit is an iron (3) gluconate complex whereas Ferrum Vitis is an iron (3) hydroxide saccharate complex.

Please replace the first paragraph on page 8 with the following paragraph:

B6

and the central nervous system. The oral lethal dose of

elemental iron varies between 200 and mg/kg. The most frequently used iron tablets are ferrosulfate (contains ~~ca.~~ about ~~20 %~~ 20% elemental iron), ferrofumarate (contains about ~~30 %~~ 30% elemental iron) or ferrogluconate (contains ~~ca.~~ about ~~10 %~~ 10% elemental iron).

Please replace the second and third paragraphs on page 9 with the following paragraphs:

The combination preparation according to the invention comprises 250 – 20,000 U of an erythropoietin preparation and 1-40 mg of an equivalent amount of iron ions of a physiologically compatible iron preparation in particular of a Fe(II) or Fe (III) complex in which the EPO preparation and the ~~ifon~~ iron preparation are present as combination preparations. Within the sense of the present invention such EPO preparations are for example used having a content of less than 2,000 U or a content of more than 7,000 U of the EPO preparation.

Within the sense of the present invention the term "combination preparations" should not only be understood as those packs of pharmaceutical products in which the EPO preparation and the iron preparation ~~ar~~ are.

Please replace the second paragraph on page 10 with the following paragraph:

Within the sense of the invention oral or parenteral forms of administration come into consideration as iron preparations. These can in principle be individual

preparations which contain a physiologically compatible iron salt or an iron complex compound as the active substance or they can also be combination preparations which, in addition to the physiologically compatible iron preparation, contain further active substances such as e.g. vitamins, folic acid, thiamine chloride, riboflavin, pyridoxine, ascorbic acid, nicotinamide, and calcium pantothenate ~~etc~~.

Please replace the second paragraph on page 12 with the following paragraph:

For the treatment of haemodialysis patients the combination preparation according to the invention comprises in particular 250 to 15,000 U (instead of the abbreviation "U" it is also possible to use the abbreviation "IU" for international units) of an EPO preparation, in particular 500 to 10,000 U. Preferred dosages are 250 U, 500 U, 1,000 U, 2,000 U, 5,000 U, 7,500 U and 10,000 U per single dose. The amount of iron ~~-ons~~ ions is preferably

Please replace the second paragraph on page 14 with the following paragraph:

When using the combination preparations it is also possible to administer the EPO preparation and the iron complex in a so-called fixed combination i.e., in a single pharmaceutical formulation which contains both compounds. These can for example be injection solutions, infusion solutions or lyophilisates which are for example filled into ampoules. This form of administration has the advantage that the EPO preparation is stabilized by the iron complex during manufacture and storage of the form of administration. The fixed combination of two active substances in the form

B10

of a lyophilisate has the further advantage of a simple and safe handling. The ~~lyophili-ate~~ lyophilate is dissolved in the ampoule by adding standard pharmaceutical injection media and administered intravenously.

Please replace the fourth paragraph on page 14 with the following paragraph:

B11

This free combination which can be provided in a single packaging unit (pharmaceutical pack) has the advantage that each patient to be treated can be individually assigned a directly ascribable amount of an EPO preparation and an iron preparation. Such combination preparations have the additional advantage of a more certain therapy success since in each case an optimally matched amount of the individual preparations is fixed and a confusion with other commercially available individual preparations that are provided in various dosages can be largely excluded. Moreover it should be ~~born~~ kept in mind that pharmaceutical preparations with different dosages are often on the market in different countries due to national requirements

Please replace the second paragraph on page 15 with the following paragraph:

B12

In the case that the EPO preparation is provided as a lyophilisate the pharmaceutical packs (combination packs) contain the appropriate amount of the EPO preparation in glass ampoules or in carpoules. The iron preparation can be present in a solid form (tablet, powder, granulate, lyophilisate, etc.) and also in a liquid form in a separate container. Furthermore the combination pack preferably contains a reconstitution solution in order to either dissolve the active substance lyophilisate alone or also together with the solid iron preparation. If the iron preparation is present as a ready-to-use solution, the solution can be mixed together with the EPO solution if it is intended to jointly administer EPO and the iron preparation. In principle the iron preparation can also be provided as a concentrate for addition to conventional infusion solutions as a result of which it is possible to administer more slowly over several hours. In this case a small volume of the solution containing

iron complex (~~ca.~~ about 0.6 – 10 ml) is added to the ready-to-use injection solution of ~~ca.~~ about 500-1000 ml.

B12

Please replace the first and second paragraphs on page 16 with the following paragraphs:

A further possibility within the sense of the present invention is to provide individual forms of administration of the erythropoietin preparation and of the iron preparation as independent pharmaceutical preparations, the individual preparations being formulated such that they contain the required amount of the individual substances of the for the combination according to the invention EPO preparation and iron complex. As a rule the pharmaceutical packs contain the prescribed package inserts which include a corresponding note regarding the combined administration with EPO or with iron preparations in the required amount. An appropriate note can also be printed on the pharmaceutical pack (secondary packaging) or on the primary packaging (ampoule, blister strip~~, etc.~~). Hence in the case of a pharmaceutical preparation containing EPO with 250 – 20,000 units EPO it is for example noted that this preparation should be in particular administered together with an iron complex preparation containing 1 – 40 mg iron, preferably 5 – 30 mg iron. Conversely in the case of iron preparations reference is made to a combined administration together with 250 – 20,000 U of an erythropoietin preparation.

B13

A further possibility of providing EPO preparations is to provide appropriate multi-dose preparations which contain the EPO preparation in larger amounts compared to individual doses. Such preparations are especially suitable for use in hospitals where many patients are treated daily. These multi-dose preparations contain the EPO preparations in doses of up to 500,000 U in particular up to ~~100,000~~ 100,000 U or 50,000 U. The advantage of the multi-dose preparations is that they enable the medical staff to take out any desired dose of the EPO preparation by for example withdrawing appropriate amounts of volume of the injectable solution. This is in particular advantageous when treating patients with different dose requirements of the active substance or when treating children who require a smaller dose of the EPO preparation. An injection solution, preferably freshly prepared at the start of the day,

B13

of for example 100,000 U of an EPO preparation could be used to treat all patients who need treatment during that day without having to prepare separate injection solutions for each individual patient. This can lead to a significant saving of time or reduction of the workload of medical staff. The individual EPO dosages are preferably withdrawn in the range of 250 U, 500 U, 1000 U and 10,000 U.

Please replace the first paragraph on page 22 with the following paragraph:

B14

The forms of administration according to the invention also enable the iron preparations to be administered 1 to 3 days before the EPO administration ~~in order~~ in order to already fill up the iron stores before the start of the EPO treatment.

IN THE ABSTRACT

Please replace the abstract with the abstract attached on a separate sheet on the following page.